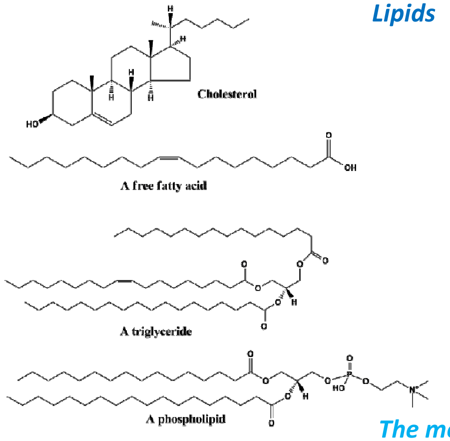
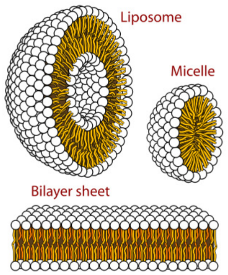
## Lipids




By Lmaps




By Mariana Ruiz Villarreal

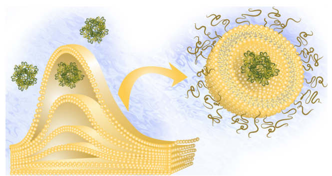
**The molecular origins of life – SoSe 2017 HD**
**Zbigniew Pianowski**

## Encapsulation – essential for life

Evolving chemical systems require compartments for Darwinian evolution – to compete, to store information and to concentrate reactants/metabolites

Encapsulation into membranes is considered an early stage in prebiotic chemical evolution and essential requirement for the emergence of life

Formation of membranes is most easy to explain among major cellular components of the prebiotic Earth. Many amphiphilic organic compounds spontaneously form vesicles in water at sufficiently high concentrations

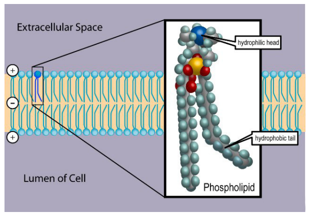


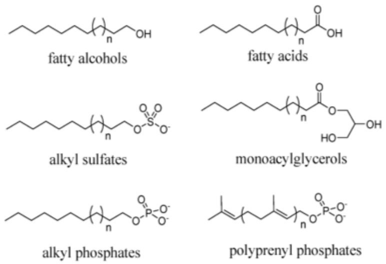
*Levine, R.M., Pearce, T.R., Adil, M., Kokkoli, E. Langmuir, 2013, 29 (29): 9208–9215.*

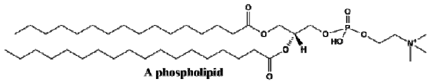
The vesicle will encapsulate an aqueous solution inside a thin layer of organic material

## Encapsulation – essential for life

Modern biological membranes consist primarly of phospholipids with embedded transmembrane proteins. Characterized by low permeability – a disadvantage during early evolution




Fatty acids and fatty alcohols are likely prebiotic lipids

## Fischer-Tropsch synthesis

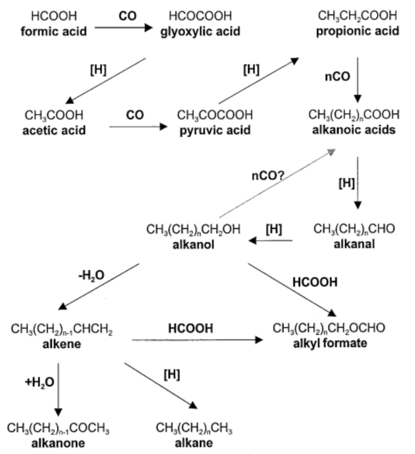
Long hydrocarbon chains from $CO + H_2$ in presence of metal catalysts and high pressure, fatty acids and alcohols are minor by-products

| Main reactions | |
|---|---|
| 1. Paraffins | $(2n+1)H_2+nCO\rightarrow C_nH_{2n+2}+nH_2O$ |
| 2. Olefins | $2nH_2+nCO\rightarrow C_nH_{2n}+nH_2O$ |
| **Side reactions** | |
| 3. Water-Gas-Shift (WGS) | $CO+H_2O\leftrightarrow CO_2+H_2$ |
| 4. Carbide formation | $yC+xM\leftrightarrow M_xC_y$ |
| 5. Alcohols | $2nH_2+nCO\rightarrow C_nH_{2n+2}O+(n-1)H_2O$ |
| 6. Boudouard reaction | $2CO\rightarrow C+CO_2$ |
| 7. Catalyst reduction and oxidation | $M_xO_y+yH_2\leftrightarrow xM+yH_2O$ |
| | $M_xO_y+yCO\leftrightarrow xM+yCO_2$ |
| 8. Coking | $H_2+CO\rightarrow C+H_2O$ |

The mixture of $D_2$ and CO over meteoritic iron or iron ore produced alkanes and n-fatty acids

*Oro, J. et al. Geochim. Cosmochim. Acta* **1976**, *40*, 915-924.

## *Hydrothermal Fischer-Tropsch synthesis*




Formic or oxalic acid heated in water at 150-250$^0$C (stainless steel reactor) yielded a mixture of $C_{12}$-$C_{33}$ lipids

*Rushdi, A., Simoneit B. Origins Life Evol. Biospheres* ***2001****, 31,* 103-118

When CO, $H_2$ and $NH_3$ are allowed to react at 200-700$^0$C in presence of Ni, Al, or clay catalysts, aminoacids are detected:

*glycine, alanine, sarcosine, aspartic acid, glutamic acid, arginine, histidine, lysine and ornithine*

Yoshino, D.; Hayatsu, R.; Anders, E. *Geochim. Cosmochim. Acta* **1971***, 35,* 927-938

## *Extraterrestrial origin of biomolecules*

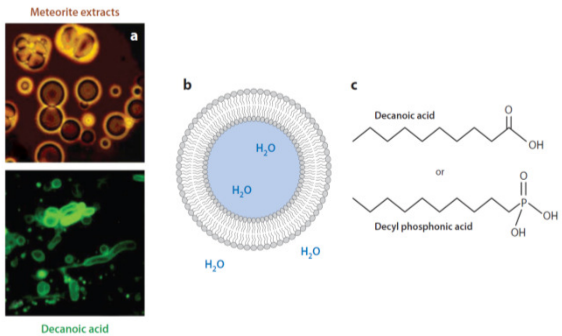
Murchison meteorite
*chondrite*

**Table 1. Soluble Organic Compounds in the Murchison Meteorite**[a]

| class of compounds | parts per million | $n$[b] |
|---|---|---|
| aliphatic hydrocarbons | >35 | 140 |
| aromatic hydrocarbons | 15−28 | 87 |
| polar hydrocarbons | <120 | 10[d] |
| carboxylic acids | >300 | 48[d] |
| amino acids | 60 | 75[d] |
| imino acids | nd[c] | 10 |
| hydroxy acids | 15 | 7 |
| dicarboxylic acids | >30 | 17[d] |
| dicarboximides | >50 | 2 |
| pyridinecarboxylic acids | >7 | 7 |
| sulfonic acids | 67 | 4 |
| phosphonic acids | 2 | 4 |
| *N*-heterocycles | 7 | 31 |
| amines | 13 | 20[d] |
| amides | nd[c] | 27 |
| polyols | 30 | 19 |

## *Encapsulation – essential for life*

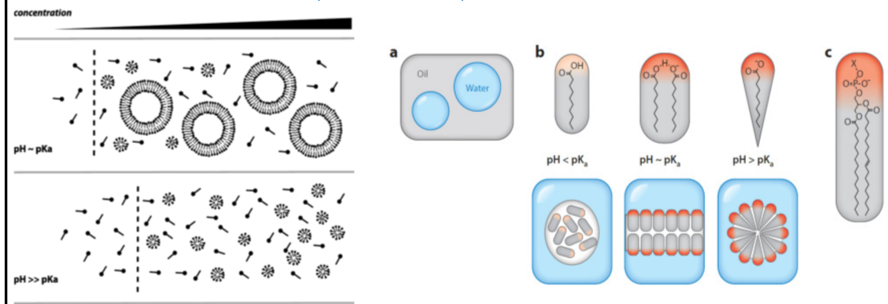
Fatty acids have been found in meteorites – plausible prebiotic synthesis pathways existed in the early Solar System




Extracts of meteorites containing these compounds spontaneously form vescicles when hydrated

## *Spontaneous generation of lipid vesicles*

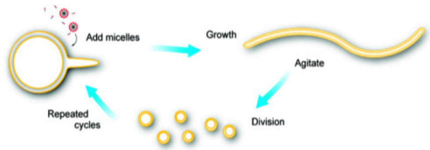
The first protocell membranes may have assembled from fatty acids and related single-chain lipids available in the prebiotic environment.




At different concentrations, fatty acids can partition between several different phases, including soluble monomers, micelles, and lamellar vesicles, with higher concentrations favoring larger vesicle aggregates.

I. Budin, A. Debnath, J. W. Szostak *J. Am. Chem. Soc.*, **2012**, 134, 20812-20819

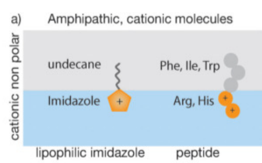
## Coupled growth and division of model protocell membranes

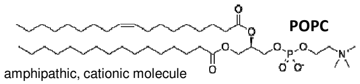



The growth of large multilamellar fatty acid vesicles fed with fatty acid micelles, in a solution where solute permeation across the membranes is slow, results in the transformation of initially spherical vesicles into long thread-like vesicles, a process driven by the transient imbalance between surface area and volume growth. Modest shear forces are then sufficient to cause the thread-like vesicles to divide into multiple daughter vesicles without loss of internal contents.


Ting F. Zhu, and Jack W. Szostak *J. Am. Chem. Soc.*, **2009**, 131 (15), 5705-5713

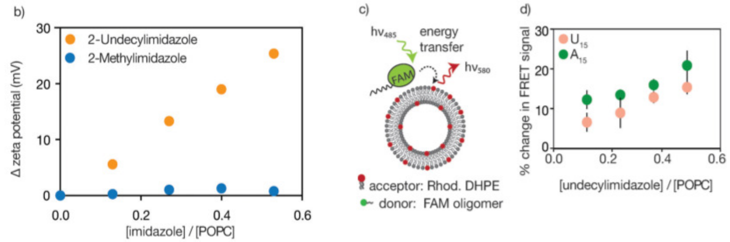
## Noncovalent nucleotide association with membranes



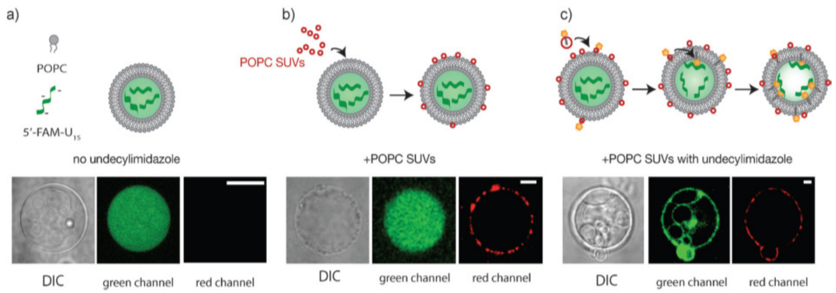

RNA localization with a model amphipathic, cationic molecule

a) Design of RNA-localizing molecules that include both nonpolar and cationic regions.
b) The change in zeta potential
c) Schematic of the FRET assay used to assess RNA localization to vesicle membranes
d) RNA (5'-FAM-$U_{15}$ and 5'-FAM-$A_{15}$) shows increasing localization to POPC membranes that contain increased amounts of undecylimidazole.




Neha P. Kamat, Sylvia Tobe, Ian T. Hill, and Jack W. Szostak *Angew. Chem. Int. Ed.* **2015**, *54*, 11735 –11739

## Noncovalent nucleotide association with membranes



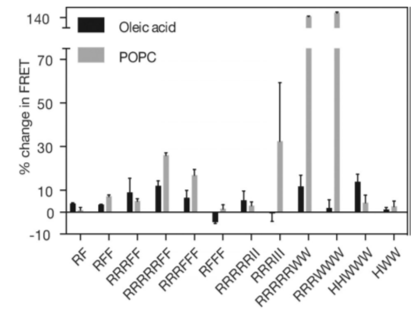

Microscopy of encapsulated RNA localization to POPC membranes with 2-undecylimidazole. Confocal images of 5'-FAM-$U_{15}$ RNA (green) association with giant POPC vesicles membranes in the presence of 2-undecylimidazole. Differential interference contrast (DIC) microscopy images are shown for each vesicle.

a) RNA appears uniformly distributed in the interior of POPC GUVs.
b) The addition of SUVs containing a rhodamine-labeled lipid (red) leads to SUV aggregation and association with the giant vesicle membranes, but RNA (green) remains uniformly encapsulated in the vesicle interior.
c) The addition of SUVs containing a rhodamine-labeled lipid (red) and 40 mol% 2-undecylimidazole leads to SUV association with vesicle membranes and RNA (green) localizes to the vesicle surface. The scale bar is 20 mm.

***SUV – small unilamellar vesicle*** ***GUV – giant unilamellar vesicle (5-25 μm)***

Neha P. Kamat, Sylvia Tobe, Ian T. Hill, and Jack W. Szostak *Angew. Chem. Int. Ed.* **2015**, *54*, 11735 –11739

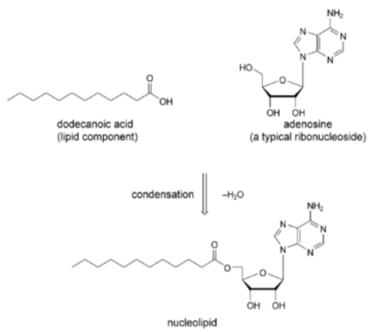
## Noncovalent nucleotide association with membranes

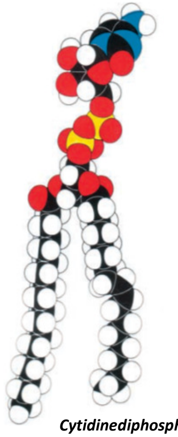


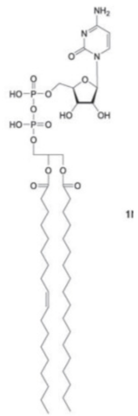

Peptide-induced RNA–membrane association. A FRET assay reports RNA localization (5'-FAM-$U_{15}$) to POPC and oleic acid membranes (7.5 mm) 10 h after the addition of 1 mm of various peptides to the vesicle solution at pH 8. Data is reported as a percentage change from control samples that lack peptide. n=4, error bars represent the standard error of the mean.

Neha P. Kamat, Sylvia Tobe, Ian T. Hill, and Jack W. Szostak *Angew. Chem. Int. Ed.* **2015**, *54*, 11735 –11739

## *Nucleolipids – a replication mechanism for genetic information?*

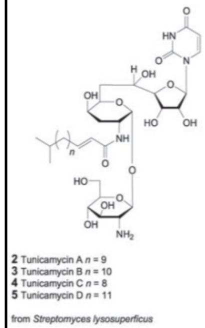


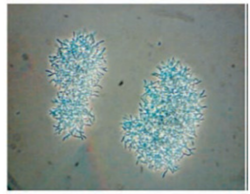





***Cytidinediphosphatediacylglicerol***

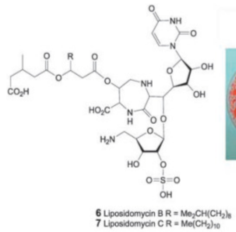
## *Antibiotic nucleolipids*

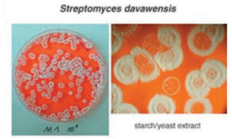


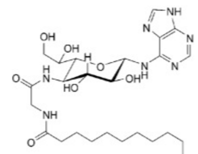



*Streptomyces lysosuperficus*

*Inhibit peptidoglycan synthesis*

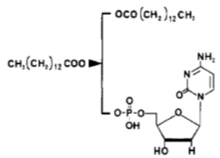


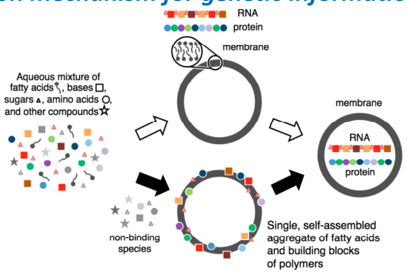



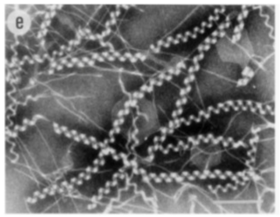
Septacidine (**8**)
from *Streptomyces fimbriatus*

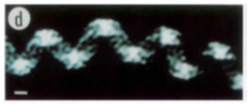
## *Nucleolipids – a replication mechanism for genetic information?*





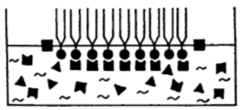

Black, R. A.; Blosser, M. C. *Life* **2016**, *6*(3), 33; doi:10.3390/life6030033





Scalebar: 200 nm

Scalebar: 10 nm



= adenine (complementary)
= thymine (noncomplementary)

*Yanagawa, H. et al. J. Am. Chem. Soc.* **1989**, *111*, 4567-4570

*Rosemeyer, H. Chem. Biodiversity* **2005**, *2*, 977

## *Phosphates*

*Source: Google Images*

*Wikimedia , Butcherbird*

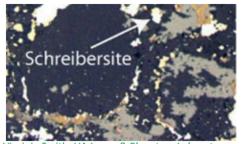
slice of the Gebel Kamil Meteorite with schreibersite rimmed by kamacite

**Schreibersite** is generally a rare iron-nickel phosphide mineral, $(Fe,Ni)_3P$, though common in iron-nickel meteorites

Acidic schreibersite corrosion under anaerobic conditions (10% aq. $HCl/N_2$) → soluble forms of phosphorus

$(Fe,Ni)_3P + HCl_{aq} \rightarrow H_2PO_3^- \rightarrow H_2P_2O_5^{2-}$

T. P. Kee *et al.Geochimica et Cosmochimica Acta.* ***2013*** *109*, 90-112

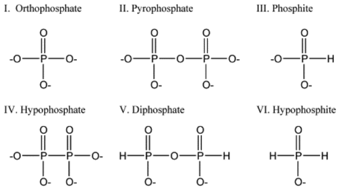


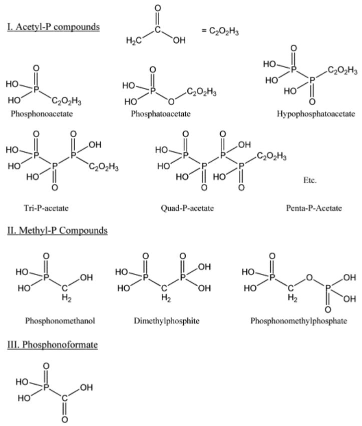


*Virginia Smith, UA Lunar & Planetary Laboratory*

Image of schreibersite grain present in a thin-section of the enstatite meteorite, KLE 98300.

## Phosphates



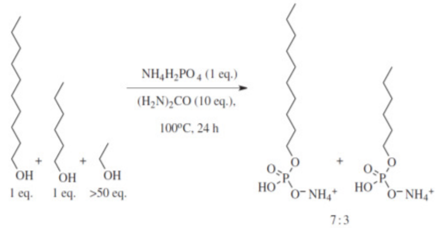




$$Fe_3P + 7H_2O \rightarrow Fe_3O_4 + H_3PO_3 + 5\tfrac{1}{2}H_2(g)$$
$$H_3PO_3 + H_2O \rightarrow H_3PO_4 + H_2(g)$$
$$2H_3PO_3 \rightarrow H_4P_2O_6 + H_2(g)$$
$$H_4P_2O_6 + H_2O \rightarrow H_4P_2O_7 + H_2(g)$$
$$H_4P_2O_7 + H_2O \rightarrow 2H_3PO_4$$

Radical pathway of the corrosion is suggested.
In presence of simple organic molecules (e.g. acetic acid) organophosphorous compounds are detected

M. Pasek *et al.Geochimica et Cosmochimica Acta.* ***2007*** *71*, 1721-1736

## Phospholipids




M. Powner, J. Sutherland *Phil. Trans. R. Soc. B* **2011**, *366*, 2870–2877

## Lipids - summary

Many amphiphilic organic compounds spontaneously form vesicles in water at sufficiently high concentrations

Current phospholipid membranes likely evolved late. Protocells probably encapsulated by fatty acids, fatty alcohols, prenyl oligomers, or phosphorylated alcohols

Nucleolipids are proposed as intermediates in templated oligonucleotide replication

Phosphorus was accessible upon corrosion of meteorite materials and could be incorporated into lipids

## The origin of small reactive intermediates

***vivianite***

*Wikimedia , Carles Millan*

**Schreibersite** $(Fe,Ni)_3P$, from iron-nickel meteorites: source of phosphorus, iron and nickel

Under more neutral conditions phosphates recombine with iron → $Fe_3(PO_4)_2$ (**vivianite**)

It should be re-solubilized to become accessible for following chemical transformations

HCN – the crucial reactive intermediate – burning of carbon-rich chondrite meteorites into redox-neutral atmosphere containing $N_2$ and water

$$Fe_3(PO_4)_2 + 18CN^-_{aq} \rightarrow 2PO_4^{3-} + 3[Fe(CN)_6]^{4-}$$

Two important functions: solubilization of phosphates and concentration of atmospheric HCN deposited as salts of mono- and divalent cations (Na, K, Mg, Ca)

Similar reactions take place with insoluble copper and nickel sulfides deposited by iron-nickel meteorite impacts (same occurence as schreibersite, rich mining sources of these metals until today)

$$NiS + H_2O + 6CN^- \rightarrow [Ni(CN)_6]^{4-} + HS^- + OH^-$$
$$Cu_2S + H_2O + 6CN^- \rightarrow 2[Cu(CN)_3]^{2-} + HS^- + OH^-$$

## The origin of small reactive intermediates

Thermal decomposition of cyanoferrates (volcanic):

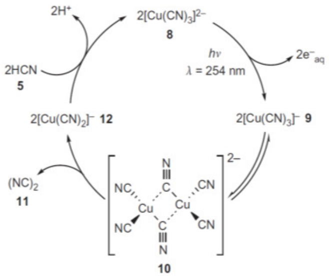
$$(Na,K)_4[Fe(CN)_6] \xrightarrow{700^oC} 4(\mathbf{Na/K)CN} + Fe(CN)_2$$
$$3Fe(CN)_2 \xrightarrow{700^oC} Fe_3C + 5C + 3N_2$$
$$Fe(CN)_2 \xrightarrow{700^oC} Fe + 2C + N_2$$

$$Ca_2[Fe(CN)_6] \xrightarrow{660^oC} 2Ca(CN)_2 + Fe(CN)_2$$
$$Ca(CN)_2 \xrightarrow{660^oC} \mathbf{CaNCN} + C \underset{}{\overset{1000^oC}{\rightleftharpoons}} \mathbf{CaC_2} + N_2$$

$$Mg_2[Fe(CN)_6] \xrightarrow{315^oC} 2Mg(CN)_2 + Fe(CN)_2$$
$$Mg(CN)_2 \xrightarrow{395^oC} MgCN_2 + C$$
$$3MgCN_2 \xrightarrow{420^oC} \mathbf{Mg_3N_2} + 3C + 2N_2$$

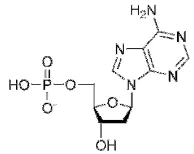
$Cu_2S + H_2O + 6CN^- \rightarrow 2[Cu(CN)_3]^{2-} + HS^- + OH^-$
cyanocuprates and $HS^-$ are delivered by this process

Photoredox cycle based on cyanocuprates may convert HCN into cyanogen

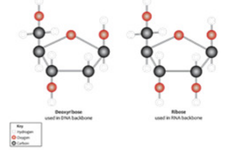


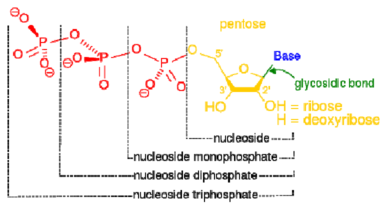

Action of water (bufferred to neutral or slightly acidic) on that mixture produced concentrated HCN solution + cyanamide (from CaNCN) + acetylene (from $CaC_2$) + ammonia (from $Mg_3N_2$)

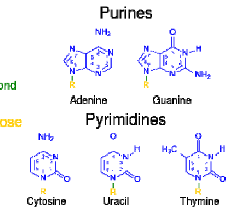
## Nucleotides - components

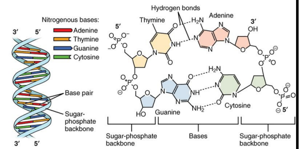


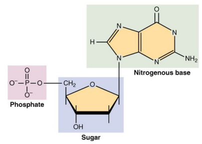
**Nucleotides = nucleobases + sugars**



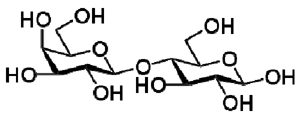


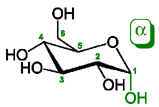



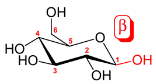




## Carbohydrates

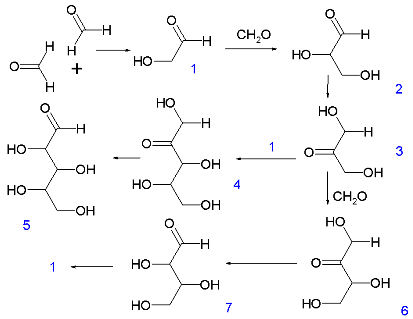


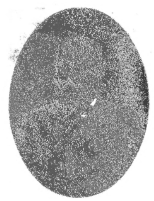







## Formose reaction



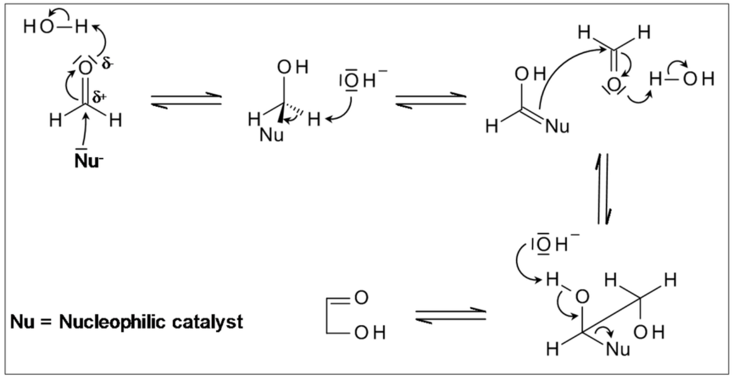



Alexander Butlerov (1828-1886)
*St. Petersburg, Kazan, Russia*

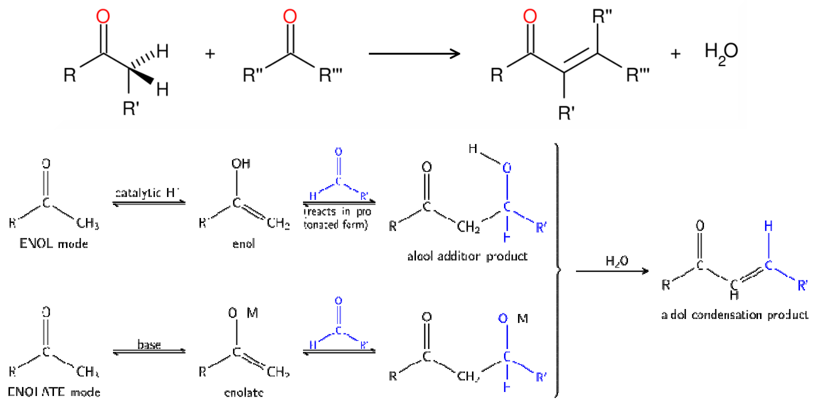
Ronald Breslow (1931-)
*Columbia University, USA*

The reaction begins with two formaldehyde molecules condensing to make glycolaldehyde **1** which further reacts in an aldol reaction with another equivalent of formaldehyde to make glyceraldehyde **2**. An aldose-ketose isomerization of **2** forms dihydroxyacetone **3** which can react with **1** to form ribulose **4**, and through another isomerization ribose **5**. Molecule **3** also can react with formaldehyde to produce tetrulose **6** and then aldoltetrose **7**. Molecule **7** can split into **2** in a retro-aldol reaction.

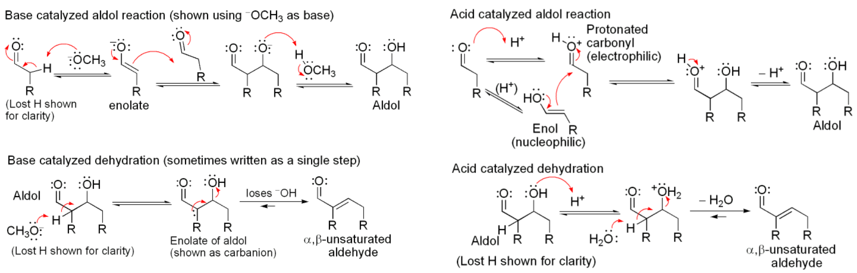
## *Formaldehyde condensation*



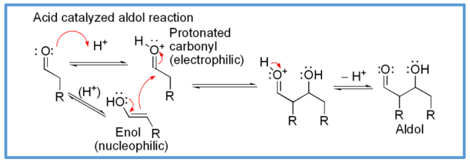

## *Aldol reaction*




## *Aldol reaction*

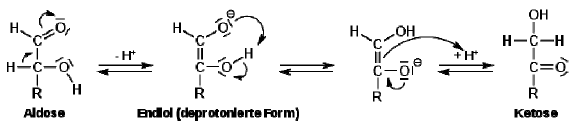



Reversible process
→ retro-aldol reaction



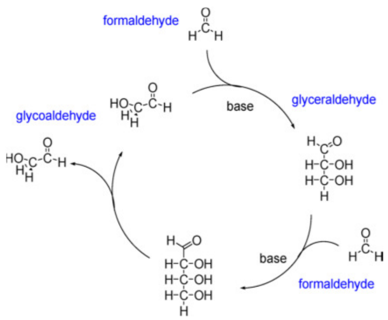

## *Aldose-ketose isomerization*

*Lobry de Bruyn(–Alberda)-van Ekenstein transformation*

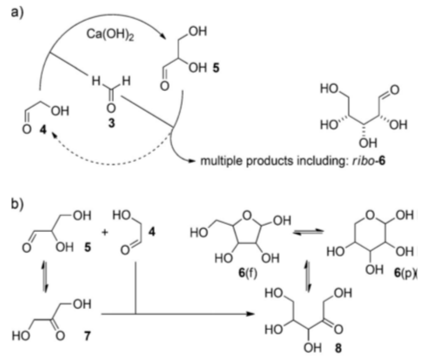


## *Formose reaction as an autocatalytic process*

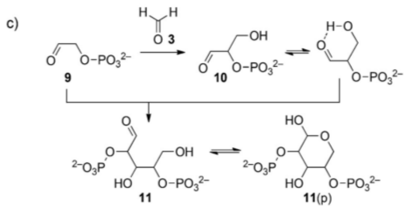
Formose reaction starts in concentrated alkaline aqueous solutions of formaldehyde
alkali are typically calcium, magnesium or lead



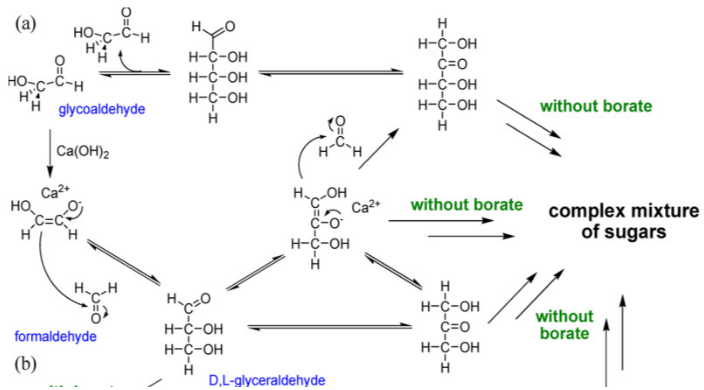

## *Formose reaction – substrate modifications*




## *Formose reaction – substrate modifications*

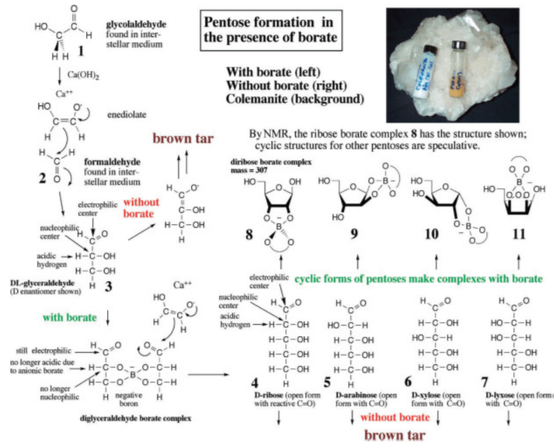



## *Formose reaction under standard basic catalysis*



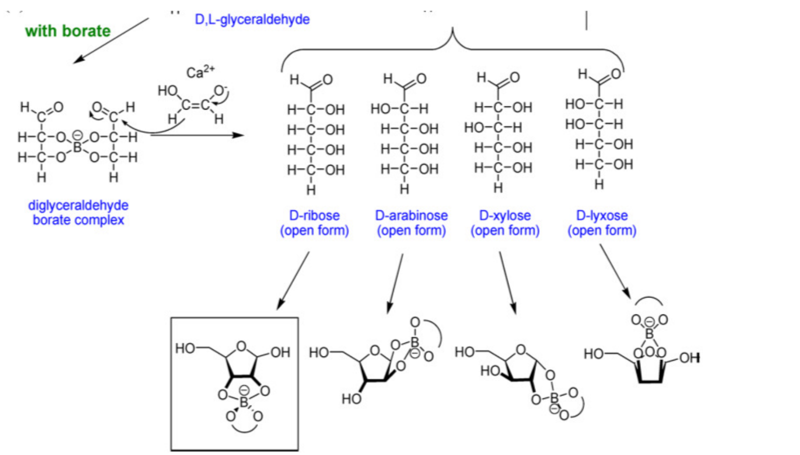

*Escosura*

## Formose reaction in presence of borates




A. Ricardo, M. A. Carrigan, A. N. Olcott, S. A. Benner *Science* **2004**, *303*, 196

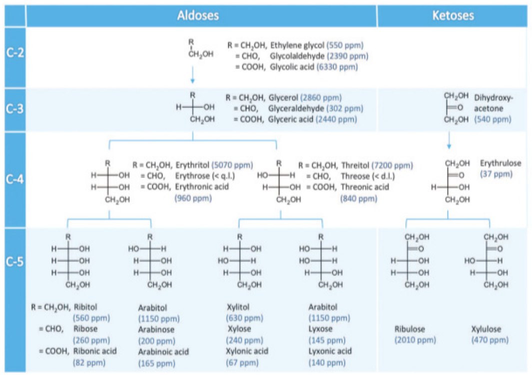
## Formose reaction in presence of borates




Escosura

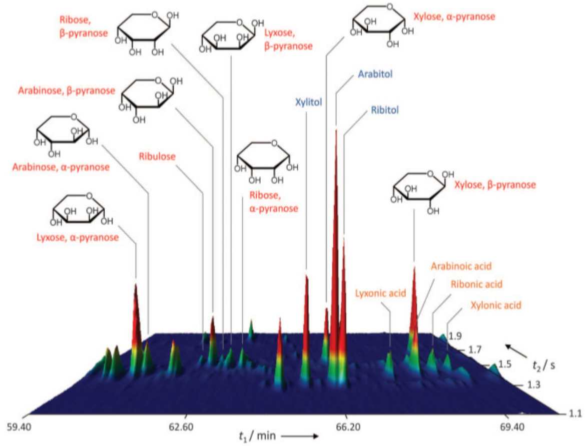
## Interstellar origin of carbohydrates

Simulations of photo- and thermochemistry of interstellar ice (silicate/carbon grains surrounded by ice $H_2O$, $CH_3OH$ and $NH_3$) exposed on UV light, low pressure ($10^{-7}$ bar) and temperature (78K) delivers a mixture of sugars



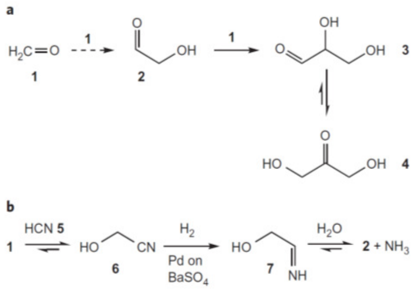

U. Meierhenrich, *et al. Science* **2016**, *352(6282)*, 208-212

## Interstellar origin of carbohydrates



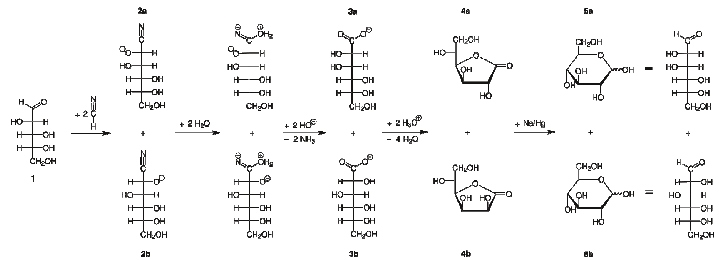

U. Meierhenrich, *et al. Science* **2016**, *352(6282)*, 208-212

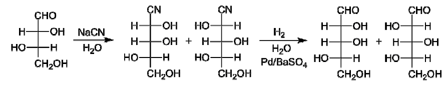
## *Prebiotically plausible alternatives to formose process*



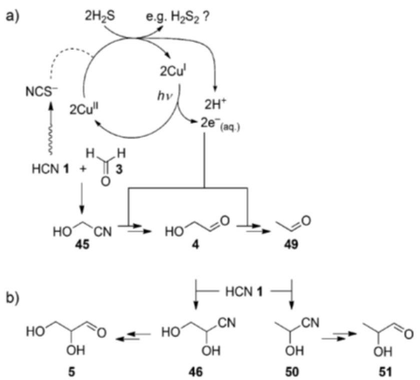
Homologation routes to simple sugars from formaldehyde **1**.
a, Direct homologation of formaldehyde **1** is problematic, because the first dimerization step (dashed) requires umpolung, and because the trimer is more stable as the ketose **4** than the aldose **3** under conditions where **3** can be formed from **1** and **2**. b, Kiliani–Fischer homologation of **1** in conventional synthetic chemistry involves favourable formation of the cyanohydrin **6** by reaction of **1** with hydrogen cyanide **5**, followed by the selective reduction of **6** using very specific conditions.

## *Kiliani-Fischer homologation*

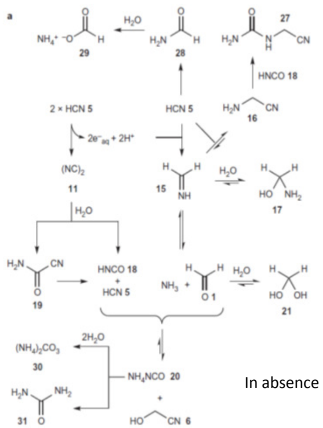


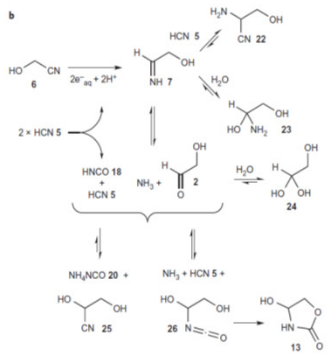


## *Cyanosulfidic chemistry for the Kiliani-Fischer homologation*



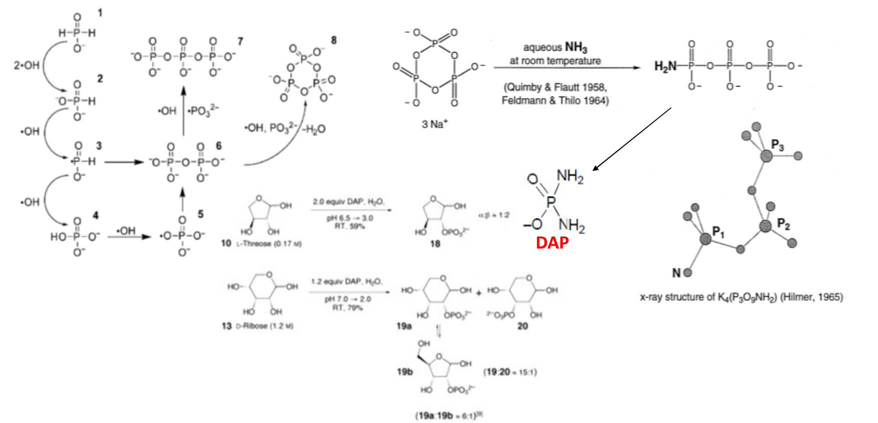
## *Cyanosulfidic chemistry for the Kiliani-Fischer homologation*





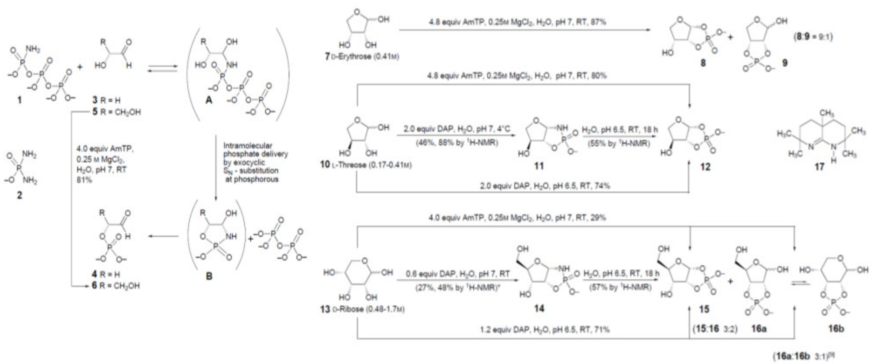
In absence of $HS^-$ glycolaldehyde **2** ends up mainly as a cyclic derivative **13**

## Phosphorylation reagents




M. A. Pasek, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 7918-7920 A. Eschenmoser, *et al. Orig. Life Evol. Biosph.* **1999**, *29*, 333-354

## Phosphorylation of sugars



A. Eschenmoser, *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2281-2285

## Carbohydrates - summary

Formose reaction gives access to numerous $C_2$-$C_5$ and higher carbohydrates, but is difficult to direct towards particular outcome, and ultimately turns into polymeric tar if overcooked

In presence of borates, the formose reaction tends to deliver protected pentoses in high yields and stable form

Although formaldehyde is the simplest starting material, the reaction is autocatalytic in glycolaldehyde and without it long incubation period is required

Carbohydrate synthesis can also occur under simulated extraterrestrial conditions – by UV-light irradiation of cometary ice

Alternative prebiotic synthesis of simple carbohydrates involves Kiliani-Fischer homologation process based on HCN in presence of copper ions and hydrosulfides – all accessible by the meteorite-derived cyanide-metal chemistry

The same type of chemistry can also deliver a set of reactive intermediates like cyanogen, acetylene, ammonia, and activated forms of phosphate – the latest can derivatize sugars and, after redox processes, deliver numerous building blocks present in currently known metabolic cycles